

Management of Hepatotoxicity in HIV-Infected Patients Treated with Combined Antiretroviral Therapy (cART): A Retrospective Cohort Study in Tianjin, China

Ping Ma^{1,3#}, Jing Qian^{1#}, Liying Gao¹, Defa Zhang¹, Aiping Yu¹, Chunting Qiu¹ and Min Wei^{2*}

¹The Tianjin Second People's Hospital, Tianjin, China

²School of Medicine, Nankai University, Tianjin, China

³Tianjin Institute of Liver Disease, Tianjin, China

#Authors contributed equally

Abstract

Background: Liver diseases are among the most frequent causes of non-AIDS-related deaths in human immunodeficiency virus (HIV)-infected patients due to hepatitis B or C virus co-infections, and/or the toxicity of long-term treatment of some antiviral drugs. There are few cohort studies reported in China.

Methods: All data from the clinic HIV/AIDS patients in the database of Tianjin Second People's Hospital, a branch of the National Free Antiretroviral Treatment Program database, from April 1, 2010 to March 31, 2016 were retrospectively assessed and analyzed.

Results: We analyzed 2270 HIV-positive, hepatitis B virus (HBV-), hepatitis C virus (HCV-) negative patients, who received cART and followed for 13334.8 person-years. A total of 67 patients (3.0%, or 5.0 per 1000 person-years) died of non-liver-related causes. The incidence of liver-related deaths in persons without HCV or HBV co-infections was zero percent during follow-up. Only 30 cases (1.3% or 2.2 per 1000 person-years) developed hepatotoxicity, but liver function of these patients improved after changing cART regimens.

Conclusion: cART-related hepatotoxicity can be well-controlled and managed by modifying the therapeutic regimens. Liver-related mortality in HIV-positive, HBV-, HCV-negative patients is currently zero percent in Tianjin, China.

Keywords: Hepatotoxicity; Combined antiretroviral therapy; HIV infection; Cohort study

Abbreviations: HIV: Human Immunodeficiency Virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; LEE: Liver Enzyme Elevation; MSM: Men who have Sex with Men; ALT: Alanine Transaminase; AST: Aspartate Transaminase; TBIL: Total Bilirubin; EFV: Efavirenz; 3TC: Lamivudine; AZT: Zidovudine; D4T: Stavudine; NVP: Nevirapine; TDF: Tenofovir

Introduction

China experienced sporadic reports in 1980s of HIV/AIDS epidemic. An outbreak in intravenous drug users (IDUs) in Yunnan province was reported in 1989 [1]. In the mid-1990s, another outbreak was reported among blood donors in central China, in the Henan and Anhui provinces. Since the late of 1990s and the early of 2000s, HIV infection has grown rapidly and has spread through out all of China [1,2]. HIV transmission also gradually shifted from intravenous-drug use to homosexual or heterosexual contact. In recent years, the prevalence of HIV infection in men who have sex with men (MSM) is rapidly increasing in the largest cities, such as Beijing, Shanghai and Tianjin [1-4]. Tianjin city is a large city, one of the four cities governed directly by central government in China. Tianjin, facing Bohai Gulf, is the eastern door of capital Beijing. All of the HIV/AIDS patients in Tianjin were treated and followed in our hospital, The Tianjin Second Peoples' Hospital (former Tianjin Infectious Disease Hospital). All of HIV-positive cases found in other hospitals in Tianjin and nearby areas were transferred to our hospital. This study will report the Tianjin's HIV/AIDS cohort.

In 2003, the Chinese government launched the China National Free Antiretroviral Therapy Program, which continues to offer anti-retroviral

agents free of charge to Chinese HIV/AIDS patients [3,4]. This program makes it easier for these patients to receive modern combined antiretroviral therapy (cART). The cART has been shown to significantly reduce the mortality of HIV/AIDS, transforming a once fatal disease into one that is more aptly described as chronic, but manageable disease. This progress, however, comes with new challenges. Side effects of cART have emerged as a major issue for HIV/AIDS treatment, and the management of anti-retroviral toxicity becomes a key focus in patient care. One of the side effects of antiretroviral agents is hepatotoxicity [5,6]. On the other hand, hepatitis virus co-infection, the great concern in Chinese HIV/AIDS infected patients, even worsen the effects of hepatotoxicity and further complicate the clinical management. The Data Collection on Adverse Events of Anti-HIV Drug (D:A:D) cohort study and the Euro SIDA observational cohort study showed that liver diseases are among the most frequent causes of non-AIDS-related deaths in HIV-positive patients [7-11]. Many deaths were related to hepatitis B virus (HBV-) or hepatitis C virus (HCV-) or both co-infections. One study from China also reported the mortality was higher in patients with triple infection or HCV-co-

***Corresponding author:** Min Wei, School of Medicine, Nankai University, No.94 Weijin Road, Tianjin, China, Tel: 0086-022-23509579; E-mail: weimin@nankai.edu.cn

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infection than those with mono-HIV-infection [3]. However, there is little research examining cART-related hepatotoxicity in the absence of HBV or HCV co-infection in HIV-infected individuals in China.

The first aim of this study was to estimate the risk of hepatotoxicity of cART in the absence of HBV or HCV co-infection in HIV-infected people, and to define other potential risk factors that may influence hepatotoxicity in this population. Secondly, we attempted to describe the effects of continuation or modification of the cART regimen according to the marker liver enzyme elevation (LEE) among these patients. Based on our results, we propose a feasible plan for the management of cART-related hepatotoxicity in such a population.

Patients and Methods

Study population

China maintains a network known as the National Free Antiretroviral Treatment Program database, which is established and managed by the National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention (China CDC). We assessed all data from the database of The Tianjin Second People's Hospital, a branch of this network, from April 1, 2010 to March 31, 2016 (data downloaded on April 16, 2016). All available data were collected, including patients' medical records, age, gender, routes of transmission, prescribed initial and subsequent cART regimens.

HIV infection status was based on positive HIV screening ELISA tests from two peripheral blood samples and confirmed by western blot. HIV test sites were certified by the National AIDS Reference Laboratory at China CDC. A diagnosis of HCV was given to patients who were seropositive for HCV or positive for HCV RNA. HBV diagnosis was assigned to patients who were positive for hepatitis B surface antigen, hepatitis B E antigen, hepatitis B core antibodies, or HBV DNA during the study period. Patients with chronic HCV infections or chronic HBV infections were excluded from this study. Patients with unknown HBV or HCV status were also excluded. The lost patients during follow-up were not included in this study. Severe alcohol use was defined according to the WHO definition of alcohol consumption, which uses >40 g/d in females and >60 g/d in males as cut-off values. Patients who were older than 18 years, treatment-naïve, and started a standard cART regimen containing two nucleoside and one non-nucleoside reverse-transcriptase inhibitors (NRTIs and NNRTIs, respectively, which is called first line regimen) were eligible for this study. All patients in this study were treated naïve, but not all were newly diagnosed.

Liver enzyme elevation (LEE) was defined as elevation of liver enzyme than normal values. In this study, the normal values of alanine transaminase (ALT) and aspartate transaminase (AST) are both 0~40 U/L. The normal value of total bilirubin (TBIL) is 1.7~17.1 μmol/L. According to Chinese National guideline of HIV/AIDS therapy, hepatotoxicity was also graded as 1, 2, 3 and 4 [12]. Grade 1 of hepatotoxicity was defined as ALT and/or AST and/or TBIL < 3 times of upper limit of normal (ULN); Grade 2 was ≥ 3 and < 5 times of ULN; Grade 3 was < 10 and ≥ 5 times of ULN; Grade 4 was ≥ 10 times ULN.

Statistical analysis

The data was input into the SPSS software and analyzed. To compare the difference before and after cART regimens, Student T test or non-parametric test- Wilcoxon test were applied accordingly.

Role of the funding source

The funder had no role in study design, data collection, data

analysis, data interpretation, or writing of the report. The author had full access to all data used in the study and had final responsibility over the decision to submit for publication. Written informed consent was obtained from each patient included in the study and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

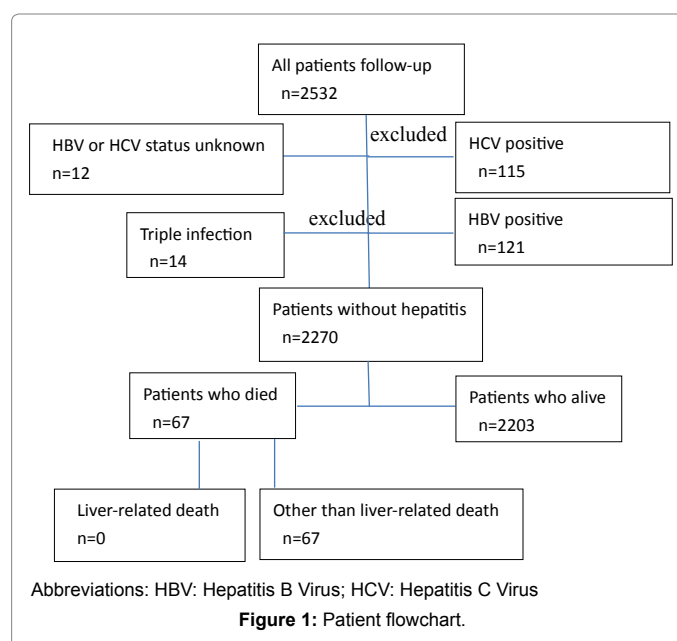
Results

Demographic and clinical characteristics of enrolled patients

We collected data for all patients enrolled from April 1, 2010 to March 31, 2016 in The Tianjin Second People's Hospital. Of total 2532 participants followed for 6 years, 115 patients (4.5%) were HCV positive, 121 (4.8%) were HBV positive, 14 (0.06%) had triple infection and 12 patients (0.05%) were HBV or HCV status unknown at the enrollment or during follow-up. The rest were all HBV and HCV negative (Figure 1). A total of HBV and HCV negative and HIV positive 2270 participants were included in this study and followed 13334.8 person-years. Among them, only 30 cases (1.3% or 2.2 per 1000 person-years) developed hepatotoxicity. Another 67 patients (3.0% or 5.0 per 1000 person-years) died of non liver-related diseases. However, nobody died of liver-related diseases. Thus, the incidence of liver-related deaths in persons without HCV or HBV was zero percent during follow-up. The non-liver related diseases include *Pneumocystis carinii* pneumonia (PCP), cryptococcal encephalitis, tuberculous meningitis, etc.

The characteristics of 30 patients who developed hepatotoxicity are listed in Table 1. Compared to 2240 patients who used the same cART regimens in the hospital, only these 30 cases developed hepatotoxicity. Our study focused on these 30 patients. The average age of these patients were 45 years (Table 1). Seventeen patients (56.67%) became infected with HIV by homosexual contact, 7 patients (23.33%) by heterosexual contact and 4 patients (13.33%) by intravenous drug use (IDU).

LEE was observed in the majority of subjects (60%) within 1 month of start of cART. After 1-3 months of cART, 7 (23.33%) patients developed LEE (Table 1). The initial cART regimens are listed in Tables 1 and 2. Except cART hepatotoxicity, other reasons could also cause



Variable	Value	%
All	30	100.00
Gender		
Male	30	100.00
Age (years)		
20-30	5	16.67
30-40	6	20.00
40-50	9	30.00
50-60	8	26.67
60-	2	6.67
Age (mean \pm SD)	43.53 \pm 12.11	
Routes of transmission		
Homosexual	17	56.67
Heterosexual	7	23.33
Intravenous drug use	4	13.33
Unknown	2	6.67
Years of follow up (mean \pm SD)	2.95 \pm 1.60	
Initial regimen		
EFV+3TC+AZT	7	23.33
EFV+3TC+D4T	3	10.00
EFV+3TC+TDF	10	33.33
NVP+3TC+AZT	9	30.00
NVP+3TC+TDF	1	3.33
CD4 (mean \pm SD) cells/ μ L	203 \pm 133	
ALT (mean \pm SD)U/L	30.57 \pm 13.13	
AST (mean \pm SD)U/L	29.87 \pm 11.81	
TBIL(mean \pm SD) μ mol/L	15.40 \pm 15.44	
LEE was observed after cART (months)		
0-1	18	60.00
1-3	7	23.33
3-6	3	10.00
6-	2	6.67
LEE was observed after cART (month, mean \pm SD)	3.6 \pm 7.5	

EFV: Efavirenz; 3TC: Lamivudine; AZT: Zidovudine; D4T: Stavudine; NVP: Nevirapine; TDF: Tenofovir; ALT: Alanine Transaminase; AST: Aspartate Transaminase; TBIL: Total Bilirubin; LEE: Liver Enzyme Elevation; cART: Combined Anti-Retroviral Therapy; SD: Standard Deviation

Table 1: Demographic and clinical characteristics of the patients with hepatotoxicity at baseline.

hepatotoxicity, such as alcohol abuse or fatty degeneration of liver. When hepatotoxicity reached grade 2 or more in these patients and we excluded other reasons, we changed their regimens (Table 2). In the initial regimens (first-line regimens), 66.67% patients used EFV-containing regimens and 33.33% used NVP-containing regimens (Table 1). In the new regimens (second-line regimens), we replaced NVP or EFV with Lopinavir and Ritonavir tablets (LPV/r) in all cases.

Comparison of liver function before and after the initial and new regimens

Because LEE is a marker for hepatotoxicity, we monitored alanine transaminase (ALT), aspartate transaminase (AST) and total bilirubin (TBIL) respectively, before and after the initial cART regimens, and after the new regimens. Table 3 lists the results. Before beginning cART, values for ALT, AST and TBIL in most patients were normal or slightly higher than normal. After start of initial cART regimens, significant elevations of ALT and AST were observed, and a small increase in TBIL was found in most of these patients. When hepatotoxicity reached grade 2 or more in these patients and we excluded other reasons, we

Patient Number	Initial Regimens	New Regimens	LEE observed (months)
1	EFV+3TC+D4T	LPV/r+3TC+TDF	4
2	EFV+3TC+D4T	LPV/r+3TC+TDF	1
3	NVP+3TC+AZT	LPV/r+3TC+TDF	0.5
4	NVP+3TC+AZT	LPV/r+3TC+TDF	0.5
5	EFV+3TC+TDF	LPV/r+3TC+TDF	1
6	EFV+3TC+TDF	LPV/r+3TC+TDF	1
7	EFV+3TC+AZT	LPV/r+3TC+TDF	24
8	NVP+3TC+AZT	LPV/r+3TC+TDF	0.5
9	EFV+3TC+TDF	LPV/r+3TC+TDF	1
10	EFV+3TC+TDF	LPV/r+3TC+TDF	6
11	NVP+3TC+TDF	LPV/r+3TC+TDF	1
12	EFV+3TC+AZT	LPV/r+3TC+TDF	6
13	EFV+3TC+D4T	LPV/r+3TC+TDF	36
14	EFV+3TC+AZT	LPV/r+3TC+TDF	1
15	EFV+3TC+TDF	LPV/r+3TC+TDF	2
16	NVP+3TC+AZT	LPV/r+3TC+AZT	1
17	NVP+3TC+AZT	LPV/r+3TC+AZT	0.5
18	NVP+3TC+AZT	LPV/r+3TC+TDF	1
19	EFV+3TC+AZT	LPV/r+3TC+TDF	3
20	NVP+3TC+AZT	LPV/r+3TC+AZT	2
21	EFV+3TC+AZT	LPV/r+3TC+TDF	3
22	EFV+3TC+TDF	LPV/r+3TC+TDF	0.5
23	EFV+3TC+TDF	LPV/r+3TC+TDF	1
24	EFV+3TC+TDF	LPV/r+3TC+TDF	2
25	NVP+3TC+AZT	LPV/r+3TC+TDF	3
26	EFV+3TC+TDF	LPV/r+3TC+TDF	1
27	NVP+3TC+AZT	LPV/r+3TC+TDF	0.5
28	EFV+3TC+AZT	LPV/r+3TC+TDF	1
29	EFV+3TC+AZT	LPV/r+3TC+TDF	2
30	EFV+3TC+TDF	LPV/r+3TC+TDF	1

LPV/r: Lopinavir+Ritonavir

Table 2: Initial and new regimens because of hepatotoxicity. changed their regimens. After the new regimens were applied, ALT, AST and TBIL values were continued to monitor after the first month, the second month and the sixth month. Within six months, the patients' ALT, AST and TBIL gradually returned back to normal levels. The values of ALT, AST and TBIL were also statistically compared. Liver function improved after one, two or six months of the application of new regimens, as shown in our statistical analyses (Table 4 and Figure 2). Thus, our data indicated that the new regimens containing LPV/r can alleviate the hepatotoxicity caused by EFV and NVP.

Notably, after the change of regimens and several months' of treatment on the new regimen, the patients' CD4+ cell counts significantly increased from 203 to 437 cells/ μ L (Table 5). None of patients died from hepatotoxicity.

The mean level of ALT and AST was 191.37 U/L and 146.83 U/L, respectively after cART exposure, but returned to normal after switching to new regimens.

The mean level of TBIL was 25.41 μ mol/L. Values returned to normal two months after switching to new regimens.

Discussion

In this retrospective cohort study, 2270 HBV, HCV negative and HIV positive patients were followed for six years (13334.8 person-years). cART-related hepatotoxicity was well-controlled, and the

	Grades	Baseline (%)	LEE exposed (%)	1 month (%)	2 months (%)	6 months (%)
ALT	normal	23 (76.67)		12 (40.00)	12 (40.00)	21 (70.00)
	Grade 1	7 (23.33)	6 (20.00)	5 (16.67)	13 (43.33)	8 (26.67)
	Grade 2		14 (46.67)	9 (30.00)	4 (13.33)	1 (3.33)
	Grade 3		9 (30.00)	3 (10.00)	1 (3.33)	
	Grade 4		1(3.33)	1 (3.33)		
AST	normal	25 (83.33)	3 (10.00)	11 (36.67)	16 (53.33)	23 (76.67)
	Grade 1	5 (16.67)	15 (50.00)	12 (40.00)	13 (43.33)	7 (23.33)
	Grade 2		5 (16.67)	5 (16.67)		
	Grade 3		5 (16.67)	1(3.33)	1 (3.33)	
	Grade 4		2 (6.67)	1(3.33)		
TBIL	normal	23 (76.67)	16 (53.33)	11 (36.67)	15 (50.00)	18 (60.00)
	Grade 1	5 (16.67)	3 (10.00)	9 (30.00)	14 (46.67)	11(36.67)
	Grade 2		5 (16.67)	7 (23.33)	1 (3.33)	1(3.33)
	Grade 3	1 (3.33)	6 (20.00)	3 (10.00)		
	Grade 4	1 (3.33)				

Grade 1, <3 times upper limit of normal; Grade 2, ≥ 3 and <5 times upper limit of normal; Grade 3, <10 and ≥ 5 times upper limit of normal; Grade 4, ≥ 10 times upper limit of normal

76% patients had normal ALT at baseline, 76% patients had grade 2-3 LEE after cART exposure. And 70% patients returned to normal after switching to new regimens and liver protection

Table 3: ALT, AST and TBIL at baseline, at the time of elevation and 1, 2, 6 months of the application of new regimens (percent).

	Time	Mean ± SD	P value
ALT	LEE exposed	191.37 ± 157.42	
	1 months	107.5 ± 102.23	0.000
	2 months	67.27 ± 56.015	0.014
	6 months	41.43 ± 24.77	0.000
AST	LEE exposed	146.83 ± 164.89	
	1 month	86.37 ± 103.87	0.000
	2 months	52.87 ± 59.56	0.05
	6 months	37.67 ± 7.74	0.217
TBIL	LEE exposed	25.41 ± 20.89	
	1 month	22.2 ± 10.12	0.624
	2 months	16.64 ± 4.73	0.017
	6 months	16.7 ± 4.04	0.909

Table 4: Non-parametric test- Wilcoxon test.

	Baseline CD4 cell count (n=30)	CD4 cell count after the treatment (n=30)	P (T test)
Patients	203 ± 133 cells/μL	437 ± 207 cells/μL	0.000

Table 5: CD4 cell count before and after the cART treatment.

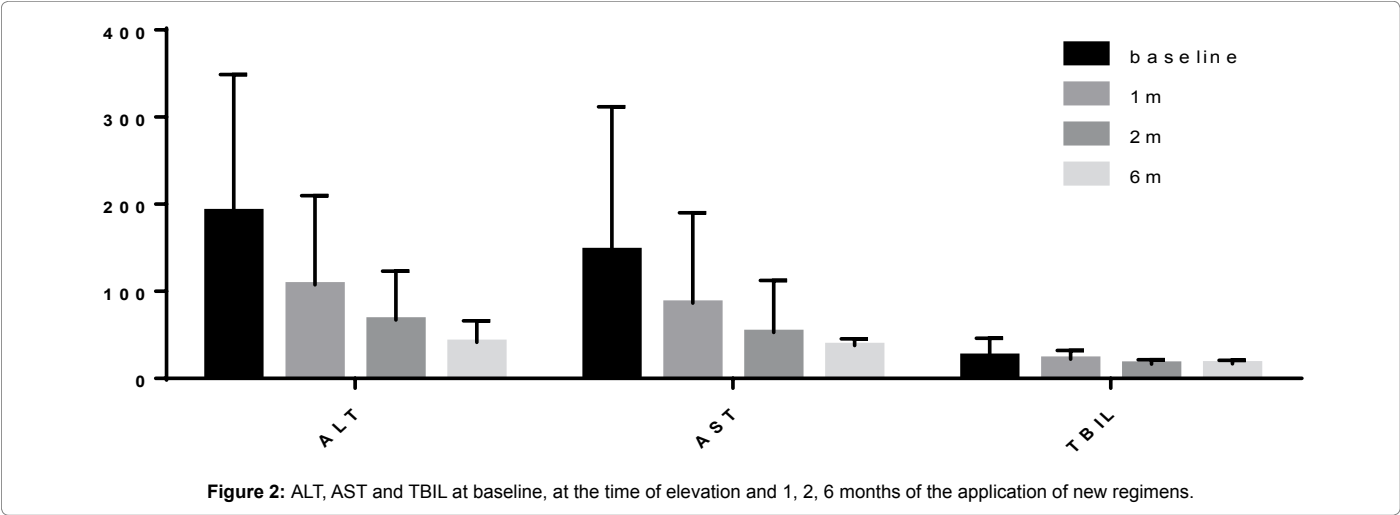


Figure 2: ALT, AST and TBIL at baseline, at the time of elevation and 1, 2, 6 months of the application of new regimens.

incidence of liver-related death was zero percent. 67 cases (3.0% or 5.0 per 1000 person-years) died of non liver-related diseases, such as PCP, cryptococcal encephalitis etc. Of 2270 patients, only 30 cases (1.3%, or 2.2 per 1000 person-years) developed LEE, mostly as a consequence of cART-related hepatotoxicity. The cART regimens of these 30 cases contained EFV and NVP. These regimens were then replaced with LPV/r-containing regimens, and the patients' liver functions progressively improved over the subsequent 6 months. LEE was mainly observed during the first 3 months of initial treatment with EFV- or NVP-containing regimens. Due to increased risk of fatal events, cART should be stopped in patients with grade 3-4 hepatotoxicity. After observing LEE in the patients, we changed their regimens. No patients died during the follow-up of this study. This finding was very similar to the French Mortavic study in 2005, in which 48 of 287 deaths (17%) in HIV-positive individuals were related to end-stage liver disease, and only 3 of 48 persons were HCV/HBV-negative [6,9].

In HIV-positive patients without HCV- or HBV- co-infection, limited data was available on liver-related mortality. In the large population-based National Health and Nutrition Examination Survey (NHANES) III study in the United States, mortality of persons with chronic HCV infection was 4.4 (1.5-12.9) per 1000 person-years [13], but liver-related mortality in HCV-negative individuals was 0.16 (95% CI, 0.10-0.25) per 1000 person years. Compared to the NHANES, our findings were zero percent among HIV-positive individuals without HCV or HBV co-infection. The reasons for this difference could be the limited cases in this study or well-managed cART regimens for the patients with high-grade hepatotoxicity.

Some studies showed that exposure to nucleoside reverse transcriptase inhibitors (NRTIs), particularly to the dideoxynucleosides (didanosine and zalcitabine), was related to the inhibition of mitochondrial DNA γ -polymerase, leading to severe hyperlactatemia and high mortality rate [14,15]. Thus, in China, these drugs are no longer recommended in the cART regimens.

Nonnucleoside reverse transcriptase inhibitors (NNRTIs) EFV and NVP, are widely used in China today, which can cause hepatotoxicity. Especially, NVP is associated with an increased risk of acute hepatotoxicity. According to national guideline [12], NVP is not used in patients with baseline CD4 cell count >250 cells/ μ L. Wang J et al. [16] reported that hepatotoxicity was significantly associated with the median NVP trough concentrations among male patients, as well as HCV- co-infection. Our study was in agreement with these findings. We have observed gradual improvement in patients' liver function after replacing EFV or NVP with LPV/r.

In some reports, the prevalence of severe alcohol use in HIV positive individuals ranges from 2.8% to 35%, depending on the observed population [17-20]. However, in this study, we didn't find any death related to alcoholic liver disease. We talked to the 30 patients who developed hepatotoxicity, and nobody reported severe alcohol use (60 g/d). This could be the life style of these patients. We also found that many patients in this cohort were MSM patients. In Tianjin and other big cities in China, MSM patients are now becoming the main population infected with HIV. They usually have good educational background and are less at risk of alcohol abuse. However, this remains speculative because of the low number of patients and this need to be further investigated.

The strength of this study is the focus on population of hepatotoxicity without hepatitis virus co-infections in Tianjin, representing other big cities of China. Limitations are that we didn't report other cART-related

side effects, which will be reported in other studies. In addition, patients totally lost in this cohort are unlikely to be on cART treatment. These missed cases are unlikely to contribute to rates of cART-related LEE.

Conclusion

In conclusion, this study provides evidence that cART-related hepatotoxicity can be controlled and managed by modifying the treatment regimens. Currently, the United States Food and Drug Administration (FDA) have approved more than 20 anti-HIV agents, and more options will likely be available in the future. In China, free cART only includes 8 therapeutic agents. Considering the risks and side effects associated with these medications, we hope that many HIV-infected patients in China will benefit from the future inclusion of additional agents in the free cART program.

Lay Summary

Hepatotoxicity caused by cART in HIV-infected patients should be monitored. Once liver function markers, such as alanine transaminase (ALT), aspartate transaminase (AST), are found higher than normal, the cART regimens should be changed accordingly to avoid the further hepatotoxicity and death to the patients.

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Author Contributions

PM, JQ and LG designed the study and decided the therapeutic regimens. DZ, AY and CQ performed the treatment to the patients and enter the data to the databank. PM and MW collected and analyzed the data. PM and MW wrote the paper.

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